REMARKS

I. Status Summary

Claims 8, 20, and 26-28 are pending in the present application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office").

Claims 8, 20, and 26-28 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the claims fail to comply with the written description requirement.

Claims 8, 20, and 26-28 have also been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the claims are indefinite.

Claims 8, 20, and 26-28 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by U.S. Patent No. 5,683,894 to Edwards *et al.* (hereinafter referred to as "Edwards").

Claims 8, 20, and 26-28 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over U.S. Patent No. 5,169,762 to Gray & Ullrich (hereinafter "Gray & Ullrich") and U.S. Patent No. 5,235,043 to Collins *et al.* (hereinafter "Collins").

Claims 8 and 26 have been amended. Support for the amendments can be found throughout the specification as filed, including at page 22 (DRG assay and EC_{50} determinations). Thus, no new matter has been added by the amendments to claims 8 and 26.

New claim 29 has been added. Support for the new claim can be found throughout the specification as filed, including particularly in claim 8 as originally filed in view of page 22 ("Biological activity of the recombinant human proNGF", the DRG assay, and EC_{50} determinations). Thus, no new matter has been added by the inclusion of the new claim.

Reconsideration of the application as amended and based on the remarks set forth below is respectfully requested.

II. Summary of the Telephone Interview

A telephone interview was conducted on May 8, 2008 between Examiner Hayes of the Patent Office and applicants' representative Christopher P. Perkins. Discussed during the interview was whether or not the instant Official Action is a Final Official Action or a Non-Final Official Action, given that the Office Action Summary page indicated that it is a Non-Final Official Action and page 8 of the Official Action indicated that it is a Final Official Action. Examiner Hayes confirmed that page 8 of the Official Action was incorrect and that the Official Action is to be considered a Non-Final Official Action.

III. Responses to the Rejections under 35 U.S.C. § 112, First Paragraph

Claims 8, 20, and 26-28 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the claims fail to comply with the written description requirement. According to the Patent Office, the specification does not support "a *pharmaceutical* preparation comprising... purified human proNGF... wherein the purified human proNGF is purified *to at least about 90% purity and has an activity in vivo analogous to β-NGF*" as recited in claim 8. Additionally, the Patent Office asserts that there is no proper antecedent basis nor conception in context with that described within the specification at the time of filing the instant application exists for the recitation of "an EC_{50} value ... that is at least about 50% of that of human β-NGF on a molar basis" in claim 26. Thus, the Patent Office contends that these phrases constitute new matter.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

III.A. Response to the Rejection as Applied to Claim 8

With respect to the rejection as applied to claim 8, applicants respectfully submit that the Patent Office is apparently requiring that the phrase at issue appear verbatim in the specification, which applicants respectfully submit is not the proper framework for analysis of written description under 35 U.S.C. § 112, first paragraph. Rather, M.P.E.P. § 2163.02 sets forth the proper analysis under this section. As indicated therein:

> Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention

as now claimed. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

Emphases added. As such, applicants respectfully submit that if one of ordinary skill in the art would have understood after review of the instant specification that applicants were in possession of the instantly claimed subject matter, then the written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied.

Applicants respectfully submit that the instant specification clearly satisfies the written description requirement. Claim 8 recites a pharmaceutical preparation comprising purified human proNGF as the active ingredient, wherein the purified human proNGF is purified to at least about 90% purity and has an activity in vivo analogous to β-NGF. One element of this claim is that the preparation is a pharmaceutical preparation. Original claim 8 recited "A pharmaceutical preparation containing recombinant proNGF as the active ingredient". Accordingly, applicants respectfully submit that one of ordinary skill in the art would understand after review of the specification that "pharmaceutical preparations" are fully supported.

Another element of claim 8 is that the pharmaceutical preparation comprises purified human proNGF as the active ingredient. Original claim 8 explicitly recites this, and thus it is clear that applicants were in possession of such a pharmaceutical preparation.

Another element of claim 8 is "wherein the purified human proNGF is purified to at least about 90% purity". Applicants have noted that page 16 of the specification describes recombinant human proNGF (rh proNGF) purified to at least about 90% purity. The Patent Office, however, asserts that page 16 discloses that inclusion bodies possess a purity of approximately 90-95% rh proNGF. But, as forth in Example 3 beginning on page 16, the instant specification describes purifying, solubilizing, refolding, and ion-exchange purification of the inclusion body material to generate biologically active rh proNGF.

To elaborate, the inclusion body starting material "always contained approx. 90-95% rh proNGF" (*see* Specification at page 16, lines 6-9). Applicants respectfully submit that the manipulations that transform the inclusion body material into the active rh proNGF involve solubilizing and refolding the inclusion body material. One of ordinary

skill in the art would understand that the solubilizing and refolding steps merely transform the biologically inactive translation product found in the inclusion bodies into a biologically active proNGF. Therefore, applicants respectfully submit that upon consideration of the specification as a whole, one of ordinary skill in the art would understand applicants to be in possession of a solubilized and refolded proNGF solution that is at least about 90% proNGF.

Another element of claim 8 relates to the activity of the proNGF relative to β-NGF. β-NGF is proNGF that has been cleaved to remove the prosequence. The Patent Office asserts that inclusion bodies cannot have an activity *in vivo* analogous to β-NGF because inclusion bodies comprise biologically inactive translation products. Applicants respectfully submit that even assuming *arguendo* that this is correct, instant claim 8 does not relate to the inclusion body material. Rather, applicants respectfully submit that claim 8 recites a pharmaceutical preparation comprising purified human proNGF as the active ingredient, wherein the purified human proNGF is purified to at least about 90% purity and has an activity in vivo analogous to β-NGF.

Thus, it is believed that one of ordinary skill in the art would understand that claim 8 relates to the biologically active proNGF, and not to the inclusion body material *per se*. Since the specification teaches that solubilization and refolding of the inclusion body material can produce the biologically active proNGF, applicants respectfully submit that one of ordinary skill in the art would also understand that it is the "activated" material to which claim 8 refers.

Applicants further respectfully submit that the specification explicitly recites that the biologically activate rh proNGF has "an activity in vivo analogous to B-NGF" (*see* Specification at pages 4-5, bridging paragraph). In this instance, since the phrase at issue appears explicitly in the specification, applicants respectfully submit that there is no basis for the Patent Office to assert that the specification does not comply with the written description requirement with respect to this element.

Summarily, applicants respectfully submit that after consideration of the specification as a whole, one of ordinary skill in the art would understand that as of the filing date of the instant application, applicants were in possession of the pharmaceutical preparation of claim 8. Therefore, applicants respectfully submit that

the instant rejection is improper, and respectfully request that it be withdrawn at this time.

III.B. Response to the Rejection as Applied to Claim 26

Next, the Patent Office asserts that there is no support for the element of claim 26 that recites "an EC_{50} value that is at least about 50% of that of human β-NGF on a molar basis". According to the Patent Office, pages 22-23 of the specification discloses that when the different molecular weights of rh β-NGF and rh proNGF are considered, the biological activity of mature rh NGF is about twice as high as that of rh NGF. The Patent Office asserts that this is different in contemplation and scope of "an EC_{50} value of 0.369 ng/ml versus 0.106 ng/ml" in a DRG assay, or "an EC_{50} value ... that is at least about 50% of that of human β-NGF on a molar basis".

Applicants respectfully disagree. Initially, applicants respectfully submit that the EC_{50} value in the context of the DRG assay is the concentration of a substance (*e.g.*, rh proNGF or rh β-NGF) that promotes the survival of half of the neurons. Thus, applicants respectfully submit that one of ordinary skill in the art would understand that an EC_{50} value represents a measure of biological activity.

In calculating how the EC_{50} values relate to the biological activities of rh proNGF and rh β-NGF, the corresponding molecular weights of these polypeptides must be considered. rh proNGF corresponds to amino acids 19-241 of GENBANK® Accession No. P01138 (*see* Specification at page 4, which discloses the SWISS-PROT Protein Sequence Database Accession No., which is the same as the GENBANK® Accession No.). Amino acids 19-241 of GENBANK® Accession No. P01138 have a predicted molecular weight of about 24.9 kDa. Mature rh β-NGF corresponds to amino acids 122-241 of GENBANK® Accession No. P01138, and has a predicted molecular weight of about 13.5 kDa. The ratio of the molecular weight of rh proNGF to rh β-NGF is 1.84. Applicants respectfully submit that if rh proNGF and rhβ-NGF had the same biological activities, the ratio of the EC_{50} value of rh proNGF to that of rhβ-NGF would also be about 1.84 since 1.84 times as much mass of rh proNGF would be needed to provide the same number of rh proNGF molecules as is provided by a given mass of rh β-NGF.

What was found, however, was that the EC_{50} value of rh proNGF was 0.369 ng/ml and the EC_{50} value of rh β-NGF was 0.106 ng/ml. The ratio between these two

EC_{50} values is not 1.84, but rather is 3.48. What that means, therefore, is that it required about twice as many rh proNGF molecules (3.48/1.84 = 1.89) to provide the same biological activity as was provided by rh β-NGF. Applicants respectfully submit that if it takes about twice as many molecules of rh proNGF to provide the same biological activity as rh β-NGF, that means that the biological activity of rh proNGF is about half of that of rh β-NGF. Similarly, applicants respectfully submit that this also means that rh proNGF has an EC_{50} value in a dorsal root ganglion (DRG) assay that is less than about twice that of rh β-NGF on a molar basis.

Applicants note, therefore, that claim 26 mistakenly indicates that the EC_{50} value of the human proNGF in a dorsal root ganglion (DRG) assay that is at least about 50% of that of human β-NGF on a molar basis. Thus, claim 26 includes a typographical error in that in fact the EC_{50} value of human proNGF is actually less than about twice that of human β-NGF. Applicants have amended claim 26 to correct this inadvertent error. Support for the amendment can be found on page 22 of the instant specification in the disclosure of the DRG assay and the EC_{50} determinations discussed hereinabove. Thus, no new matter has been added by the amendment to claim 26.

Accordingly, applicants respectfully submit that the instant rejection of claim 26 under the written description requirement of 35 U.S.C. § 112, first paragraph, has been addressed. Applicants respectfully request that that the instant rejection be withdrawn at this time.

IV. Response to the Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 8, 20, and 26-28 have also been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the claims are indefinite. Particularly, the Patent Office asserts that the phrases "at least about 90%", "at least about 50%", and "activity analogous to β-NGF" are ambiguous.

Applicants respectfully disagree. Initially, applicants respectfully submit that claim 26 has been amended to delete the phrase "at least about 50%", and thus the rejection with respect to this phrase is believed to be moot.

Turning now to the phrase "at least about 90%", applicants respectfully traverse the Patent Office's assertion that the limitation "at least" removes any lower limit below

90%. Rather, applicants respectfully submit that the phrase "at least" modifies about 90%, not 90% itself. Given that the Patent Office has acknowledged that the phrase "about 90%" would be understood by one of ordinary skill in the art, applicants respectfully submit that one of ordinary skill in the art would also understand the metes and bounds of the phrase "at least about 90%".

Nonetheless, in an effort to facilitate prosecution, applicants have amended claim 8 to remove the term "about" from the phrase "at least about 90%". Applicants respectfully submit that the amendment to claim 8 addresses the instant rejection under 35 U.S.C. § 112, second paragraph, and respectfully request that it be withdrawn at this time.

Turning now to the phrase "activity analogous to β-NGF", the Patent Office has suggested that amending claim 8 to recite "and promotes survival of DRG sensory neurons" would obviate the rejection. Applicants have amended claim 8 in accordance with this suggestion, and thus believe that the instant aspect of the current rejection has been addressed.

Summarily, applicants respectfully submit that the amendments to claims 8 and 26 address all aspects of the rejections of claims 8, 20, and 26-28 under 35 U.S.C. § 112, second paragraph. Applicants respectfully request that the instant rejections be withdrawn at this time.

V. Response to the Rejection under 35 U.S.C. § 102(b)

Claims 8, 20, and 26-28 stand rejected by the Patent Office upon the contention that these claims are anticipated by Edwards. According to the Patent Office, Edwards discloses the "whole prosequence" of proNGF.

After careful consideration of the rejection and the Patent Office's bases therefore, applicants respectfully traverse the rejection and submit the following remarks.

In order to support a rejection under 35 U.S.C. § 102(b), a single prior art reference must describe, either expressly or inherently, each and every element as set forth in the claim. *See* M.P.E.P. § 2131, *citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claim 8 presently recites a pharmaceutical preparation comprising purified human proNGF, wherein the purified human proNGF (a) is the active ingredient; (b) is purified to at least 90% purity; (c) has an activity *in vivo* analogous to β-NGF; and (d) promotes survival of dorsal root ganglia (DRG) sensory neurons. Applicants respectfully submit that Edwards does not disclose these elements.

In support of the instant rejection, the Patent Office asserts the following:

- Edwards teaches how to make a pharmaceutical composition comprising a recombinant pro-NGF-beta solution "derived from humans" (*e.g.*, col. 4, lines 40-42), which inherently comprises SEQ ID NO: 4 and inherently is encoded by a nucleic acid comprising SEQ ID NO: 3 (claims 20, 27, 28);
- Example 2 teaches *in vitro* translated proNGF (*i.e.*, including proNGF from human, murine, bovine; col. 4, line 41), which would reasonably be purified to at least 90% purity based on this translation system (claim 8); and
- that proNGF produced by such a procedure inherently has whatever activity it possesses based on its structural characteristics (claim 26).

Applicants respectfully traverse these assertions. Applicants respectfully submit that Edwards does not teach a pharmaceutical preparation of human proNGF that is at least 90% pure, has an activity *in vivo* analogous to β-NGF, and promotes survival of dorsal root ganglia (DRG) sensory neurons as recited in claim 8. Rather, applicants respectfully submit that Edwards has produced only murine proNGF and NGF-β. There is no disclosure in Edwards of any form of human proNGF other than as a starting material to be cleaved to form compositions comprising mature NGF-β.

To elaborate, the only discussions of pharmaceutical compositions in Edwards relate to pharmaceutical compositions of mature NGF-β. This can be seen at col. 5, line 49 through col. 6, line 29, which disclose administration of NGF-β, encapsulated NGF-β, lyophilized preparations of NGF-β, and amounts of NGF-β that are required to treat particular neural disorders. Additional references to pharmaceutical preparations can be found in Example 8, which discloses injectable formulations of NGF-β and NGF-β "depot" formulations. Applicants respectfully submit that Edwards defines "NGF-β" to be "the pure, active, mature beta subunit of 7S NGF" (*see* col. 3, lines 33-34. Therefore,

applicants respectfully submit that each and every reference to a pharmaceutical preparation in Edwards relates to preparations of pure, active mature NGF-β. As a result, applicants respectfully submit that Edwards does not disclose any pharmaceutical preparations of proNGF.

Furthermore, applicants respectfully submit that Edwards explicitly discloses that proNGF had little or no activity in the DRG assay (*see* Example 6 of Edwards). Therefore, applicants respectfully submit that the explicit language of Edwards expressly contradicts the Patent Office's assertions with respect to the disclosures of these references.

Furthermore, applicants respectfully submit that the Patent Office's assertion that the activity of proNGF is inherent from its structural characteristics (presumably referring to its primary amino acid structure) is also explicitly contradicted by the disclosure of Edwards. First, applicants respectfully submit that Edwards discloses in Example 6 that two forms of proNGF had "little or no activity" in the DRG assay, whereas digestion of either of these forms with trypsin resulted in "substantial NGF-β activity". Therefore, the proNGF produced by the mouse L929 cells as set forth in Example 6, despite presumably having the proper primary amino acid sequence of murine proNGF, was non-functional.

Secondly, Edwards explicitly discloses in col. 3, lines 3-15 that *in vitro* translated proNGF was aberrant in several respects. According to Edwards, "when NGF-beta mRNA obtained from mouse submaxillary gland was translated in cell-free expression systems, anti-NGF IgG failed to precipitate significant amounts. Some precipitate ensued when the mRNAs were translated cell-free in the presence of anti-NGF IgG, however, no biological activity was reported" (Edwards at col. 3, lines 4-9; emphases added). Additionally, Edwards further discloses that "expression of the pro-NGF-beta polypeptide in cell-free systems results in an improperly-folded protein, which is degraded rather than cleaved to active form by NGF-gamma" (Edwards at col. 3, lines 12-15; emphasis added).

Taken together, these statements expressly rebut the Patent Office's contention that *in vitro* translated proNGF, even if it were purified to at least 90% purity, would be

expected to have any biological activity at all, let alone a biological activity *in vivo* that is analogous to β-NGF as recited in claim 8.

And finally, applicants respectfully submit that the Patent Office's reliance on M.P.E.P. § 2123 is misplaced in the context of the instant rejection. According to the Patent Office, "[t]he use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain", and that "[a] reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments". It appears that these quotations come from several cases decided by the Court of Appeals for the Federal Circuit: *In re Heck*, 699 F.2d 1331, 1332-33 (Fed. Cir. 1983); *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, (Fed. Cir. 1989), *cert. denied*, 493 U.S. 975 (1989); *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323 (Fed. Cir. 2005); and *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998).

These cases fall into two broad categories: *Merck* and *Heck* are cases that involve the prior art effects of patents in the context of 35 U.S.C. § 103. Thus, they do not support the instant rejection, which is a rejection under 35 U.S.C. § 102.

Upsher-Smith and *Celeritas* relate to issues wherein the later claimed subject matter was explicitly disclosed in the prior art reference, but that the prior art reference taught away from the later claimed subject matter. Applicants respectfully submit that these cases also fail to support the instant rejection because Edwards does not explicitly disclose pharmaceutical preparations comprising purified human proNGF as the active ingredient, wherein the purified human proNGF is purified to at least 90% purity and has an activity in vivo analogous to β-NGF and promotes survival of dorsal root ganglia (DRG) sensory neurons as recited in claim 8. Therefore, applicants respectfully submit that even when viewed in the context of M.P.E.P. § 2123, Edwards fails to support the instant rejection because Edwards does not disclose the subject matter of claim 8.

Summarily, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of anticipation of claim 8 over Edwards because Edwards

does not disclose each and every element of claim 8. Claims 20 and 26-28 all depend from claim 8, and thus are also believed to be distinguished over Edwards. Accordingly, applicants respectfully request that the rejection of claims 8, 20, and 26-28 over Edwards be withdrawn at this time.

VI. Response to the Rejection under 35 U.S.C. § 103(a)

Claims 8, 20, and 26-28 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Gray & Ullrich and Collins.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

In support of the instant rejection, the Patent Office asserts that Gray & Ullrich teach both the amino acid and nucleotide sequence of human proNGF, methods of making NGF proteins recombinantly using either prokaryotic or eukaryotic host cells, and pharmaceutical compositions thereof. The Patent Office concedes, however, that Gray & Ullrich are silent regarding the activity of proNGF as it relates to β-NGF. The Patent Office asserts, however, that the activity of proNGF is directly related to its structure, and therefore, is an inherent property of proNGF.

The Patent Office's attention is directed to the discussion hereinabove wherein the shortcoming of this inherency argument vis-à-vis the biological activity of proNGF has been discussed. Summarily, applicants respectfully submit that Edwards explicitly discloses that *in vitro* translated and recombinant forms of proNGF have no activity and/or fold incorrectly to produce an inactive polypeptide. As a result, there is believed to be clear scientific evidence in the record that biological activity for proNGF is not an inherent property based merely on primary structure, and thus the Patent Office's inherency argument fails as a matter of law (*see* M.P.E.P. § 2163.07(a): "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient"; *citing In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999); emphases added).

Therefore, since the instant claims relate to pharmaceutical preparations comprising human proNGF as the active ingredient, the Patent Office's concession that

Gray & Ullrich are silent regarding the activity of proNGF as it relates to β-NGF in view of the fact that recombinant and *in vitro* transcribed proNGF preparations do not inherently possess activity is clear evidence that Gray & Ullrich's disclosure of the amino acid and nucleotide sequences of human proNGF is insufficient to support the instant rejection because it provides one of ordinary skill in the art with no reasonable expectation that a human proNGF preparation *per se* would have any activity whatsoever. As such, applicants respectfully submit that there is no suggestion in Gray & Ullrich to produce a pharmaceutical preparation with human proNGF as the active ingredient.

Applicants further respectfully submit that Collins fails to cure this deficiency. According to the Patent Office, Collins teaches "production of purified forms of all members of the NGF/BDNF family of neurotrophic proteins which would be valuable as pharmaceutical preparations" as well as biologically active recombinant human NGF family member proteins. Here as well, however, the Patent Office concedes that Collins is silent regarding the activity of proNGF as it relates to β-NGF, again asserting that the activity of proNGF is directly related to its structure, and therefore, is an inherent property of proNGF. Given the fact that the prior art of record has established that recombinant and *in vitro* translated forms of proNGF do not necessarily have biological activity, the Collins reference, like Gray & Ullrich, does not satisfy the requirements of inherent disclosure.

Furthermore, applicants submit herewith several scientific publications that are believed to demonstrate that there are significant structural and mechanistic differences between β-NGF and the uncleaved, pro-form of nerve growth factor, proNGF. These publications also disclose that an activity of proNGF or an effect that is caused by proNGF cannot be predicted from the β-NGF activity or from the structure of β-NGF.

For example, Kliemannel *et al.* (2007) 16 *Protein Science* 411-419, a copy of which is being submitted herewith as **Exhibit D**, shows that a part of the sequence of proNGF (*e.g.*, the pro-sequence) competes with native β-NGF for receptor binding, resulting in a lowered affinity of proNGF to both receptors (*see e.g.*, page 417, paragraph bridging left and right columns). The activity is lowered 7 to 20-fold (*see* page 843, final paragraph of Nykjaer *et al.* (2004) 427 *Nature* 843-848, a copy of which is

being submitted herewith as **Exhibit E**). This demonstrates that the presence of the pro-sequence disturbs the interaction of the NGF sequences with NGF receptors, presumably by interacting with Trp-21, which also is involved in receptor binding by the mature NGF (*see* **Exhibit D**, Abstract).

Thus, applicants respectfully submit that if the protein acts via different pathways, the activity cannot be the same as NGF. In addition, the structure is different from NGF. There is no "inherent" activity of pro-NGF for receptor binding. Also, **Exhibit E** describes a receptor called sortilin that is bound exclusively by proNGF and not by NGF, which applicants respectfully submit is evidence of a different activity spectrum of proNGF. ProNGF binds with much higher affinity to sortilin than does NGF (5 nM versus 87 nM).

Additionally, Boutilier *et al.* (2008) 283 *J Biol Chem* 12709-12716, a copy of which is being submitted herewith as **Exhibit F**, discloses that inhibiting endocytosis or furin activity reduced TrkA receptor activation induced by proNGF. On the other hand, inhibiting endocytosis or furin activity did not reduce receptor activation that was induced by mature NGF. The authors concluded that endocytosis and cleavage appear to be prerequisites for proNFG-induced TrkA receptor activity.

Taken together, applicants respectfully submit that these data indicate that under physiological conditions, proneurotrophins do not directly bind or activate Trk receptors. However, endocytosis and cleavage of proneurotrophins produce processed forms of neurotrophins that are capable of inducing Trk activation. Applicants respectfully submit that this is believed to show that pro-neurotrophins, including proNGF, have activities that are different from and independent of NGF.

Considering these documents, applicants respectfully submit that prior to the instant disclosure, one of ordinary skill in the art would have had no expectation of success and no basis for believing that proNGF would have an activity similar or analogous to β-NGF. Therefore, applicants respectfully submit that the combination of Gray & Ullrich and Collins does not support a *prima facie* case of obviousness of claim 8 because the combination does not disclose or suggest each and every element of the claims.

And finally, applicants respectfully reiterate that instant claim 8 recites that the human proNGF is the active ingredient in the pharmaceutical preparation. As such, even assuming *arguendo* that one of ordinary skill in the art might have generated proNGF as a prodrug, the art of record clearly establishes that there is no reasonable expectation that the proNGF in any such preparation would itself be active. Rather, applicants respectfully submit that the only evidence that human proNGF *per se* has any biological activity that would motivate one of ordinary skill in the art to generate a pharmaceutical composition comprising human proNGF as the active ingredient is found in applicants' own specification. Accordingly, applicants respectfully submit that the Patent Office's is employing impermissible hindsight in concluding that one of ordinary skill in the art would have been motivated to produce a pharmaceutical preparation comprising human proNGF as the active ingredient.

Summarily, applicants respectfully submit that the combination of Gray & Ullrich and Collins does not support a *prima facie* case of obviousness of claims 8, 20, and 26-28. Accordingly, applicants respectfully request that the instant rejection be withdrawn at this time. Applicants further respectfully submit that claims 8, 20, and 26-28 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

VII. Discussion of the New Claim

New claim 29 has been added. Support for the new claim can be found throughout the specification as filed, including particularly in claim 8 as originally filed in view of page 22 ("Biological activity of the recombinant human proNGF", the DRG assay, and EC_{50} determinations). Thus, no new matter has been added by the inclusion of the new claim.

Applicants respectfully submit that claim 29 is believed to be distinguished over the cited references for the reasons set forth hereinabove with respect to the pending rejections. As such, claims 8, 20, and 26-29 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment of fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: June 19, 2008

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